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CLINICAL EVOLUTION AND TREATMENT OPTIONS IN CONGENITAL ANOMALIES OF KIDNEY AND URINARY TRACT IN CHILDREN

ABSTRACT

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KEYWORDS: congenital anomalies of the kidney and urinary tract, CAKUT, urinary tract infection, vesicoureteral reflux, hydronephrosis

INTRODUCTION

The chosen topic consists of a complex malformative pathology, frequent in pediatric patients, which is sometimes difficult to understand by the patient and family.

Graphical representation is often an easy and effective way of communication between doctor and patient. Understanding the mechanisms of the disease leads to good physician-patient communication, increases adherence, patient monitoring, and treatment.

Medical collaboration is useful in understanding the need for specific monitoring of these patients by a pediatric nephrologist and leads to an improved prognosis.

Congenital kidney and urinary tract defects are a heterogeneous group of diseases, also known as congenital kidney and urinary tract abnormalities (CAKUT). CAKUT are an important cause of morbidity and mortality in the pediatric population, being some of the most common birth defects. CAKUT covers a wide range of conditions ranging from mild, asymptomatic malformations that require only periodic monitoring up to severe malformations with life-threatening potential, requiring emergency medical and/or surgical intervention.

The mammalian kidney acts as a regulator of water balance, in acid-base and electrolytic homeostasis, and the excretion of catabolism products. These activities depend on the development of specific cells in a well-established temporo-spatial pattern and the formation of a sufficient number of nephrons. Defects in the development of these molecular structures lead to the development of CAKUT, which is the leading cause of chronic kidney disease (CKD) in the pediatric population.

The development of the human kidney begins in the fifth week of intrauterine life with the formation of new nephrons. This process is continuous until 32-34 weeks of gestation. After this period, no new nephrons are formed, but the growth and development of existing nephrons continue. Thus, the number of nephrons is already established at birth, the reduction of their number during life through renal injury may cause progressive degradation of renal function.

Prenatal diagnosis of CAKUT is made by fetal ultrasonography (US) at the age of 18-20 weeks of gestation. A significant percentage of the cases of hydronephrosis diagnosed antenatally have a transient character, being of a physiological nature. Postnatal abdominal US is used as a screening method in patients with urinary tract infections (UTI) to identify CAKUT.

The clinical manifestations of these types of malformations vary, many of them being asymptomatic, which is why the diagnosis is often accidental. Clinical symptoms may be general including abdominal pain, palpable abdominal mass, abdominal distension, or lumbar discomfort. Infectious complications, such as UTIs, are often symptomatic, with the patient having dysuria, abdominal pain, fever, refusal of food, nausea, and vomiting.

There is no specific treatment for malformations, but infectious complications require prompt and effective drug treatment to prevent renal injury. Surgical treatment is reserved for cases of severe obstruction, severe alteration of unidirectional urinary flow, or complex malformations. The surgical treatment aims to ensure the permeability of the urinary tract and the efficient, unidirectional evacuation of urine as well as the protection of the renal parenchyma.

Infectious complications account for a significant share of morbidity in patients with CAKUT, requiring increased attention and prompt treatment. CAKUT is the leading cause of CKD in children. Late diagnosis, repeated renal scarring due to infectious complications and the negative effects of the renal urinary stasis may aggravate the degree of CKD. Therapeutic goals are CKD prevention, and if this is not possible, delaying CKD in pediatric patients with CAKUT and providing individualized treatment options.

OBJECTIVES

This paper aims to:

- Describe different types of reno-ureteral malformations, bringing data from the literature on the current level of knowledge in the field;
- Alert about the risk of complications and the need for frequent monitoring of these patients depending on the severity of the condition;
- Provide therapeutic options in accordance with customized international guidelines for CAKUT;
- support the prevention of CKD, and if that is not possible, acknowledge the best possible management and therapeutic options for a pediatric patient with CAKUT;
- Exemplify the existence of CAKUT in the pediatric population through a significant study group of 252 pediatric patients, whose evolution was monitored per specified time unit;
- Exemplify the risks and offer therapeutic options for patients with CAKUT who associate urinary tract infections by establishing a local antibiotic resistance pattern;
- Develop a diagnostic algorithm for pediatric patients with CAKUT.

PERSONAL CONTRIBUTIONS

The current study consists of a retrospective study of 252 pediatric patients identified with CAKUT, and a cross-sectional analytical study that included 91 patients with CAKUT that developed at least one episode of UTI. The patients with reno-ureteral malformations hospitalized within the Emergency Hospital for Children "Louis Țurcanu" Timișoara were identified from the total of observation sheets analyzed for a period of 30 months. The 252 patients had 309 malformations, some patients with isolated renal or ureteral malformations, while others had two or even more malformations simultaneously.

We included in the study patients aged 0 to 18 years who had at least one malformation regarding the reno-ureteral system and identified by abdominal US examination. We excluded patients with secondary causes of hydronephrosis (external compression or lithiasis) and patients undergoing cytostatic or immunosuppressive treatment for oncological conditions.

We retrospectively analyzed the electronic files of 42020 patients admitted to the Emergency Hospital for Children "Louis Țurcanu" Timișoara for a period of 30 months (between January 2015 and June 2017) and identified 252 pediatric patients with reno-ureteral malformations included in the current research - study 1.

Study group 1, comprising 252 patients, was monitored for 5 years and patients with complications were identified. Patients with infectious complications, such as UTI, confirmed by positive urine culture, were analyzed separately in study 2 for the antibiotic resistance of the causative germs.

We analyzed the frequency of CAKUT according to age, sex, area of origin. Regarding the timing of the initial diagnosis of malformations, four possibilities were considered:

- antenatal diagnosis by fetal ultrasonography;
- perinatal diagnosis by screening in the first 30 days after birth;
- CAKUT diagnosis with the occasion of concomitant infectious factor, respectively UTI;
- accidental diagnosis by an abdominal US: either by screening procedures or other diagnoses, unrelated to the reno-urinary tract.

The laboratory tests of interest for the current study were: urea, creatinine, uric acid, urine test, urine culture.

The abdominal US performed at the Emergency Hospital for Children "Louis Țurcanu" Timișoara was a study inclusion criteria. Additional imaging investigations included mictional cystography, in some cases. Depending on the location, we classified CAKUT into renal, ureteral, and bladder/subvesical malformations. We analyzed the frequency of unilateral left/right impairment, bilaterality correlated with age group, sex, background, and time of diagnosis.

We identified the association of CAKUT with malformations of other organs and systems, comparing the data obtained with the data present in the literature.

Regarding the therapeutic options of patients with CAKUT, we analyzed etiological treatment of UTI, as well as UTI prophylaxis and surgical treatment.

CAKUT complications were consisting of two main categories: infectious complications and renal degenerative complications – CKD. Out of the 252 patients with CAKUT included in the study, 91 patients developed 260 positive urinary tract infections. We further investigated the antibiotic resistance patterns of uropathogens causing UTI in pediatric patients with CAKUT. CKD was present in 33 of the study patients.

GENERAL CONCLUSIONS

CAKUT in the pediatric population is one of the most common types of malformations of the child.

The present research aimed to describe and analyze the types of reno-ureteral malformations encountered in the pediatric population and to identify their evolution patterns, as well as identify ideal therapeutic options. The present study matches other studies of national-level related to the distribution of CAKUT in the pediatric population, but also brings unique data on the antibiotic resistance of uropathogens causing UTI in children with malformations of the urinary tract.

Based on these data, we can draw a series of conclusions that result from current research and have as main objective CAKUT awareness, identification of risk factors in the development of complications, and highlights useful therapeutic methods:

- Most of the children included in the study group (51.58%) were over 3 years old at the time of diagnosis;
- Over 50% of the group's patients came from urban areas (53.57%);
- The prenatal diagnosis was performed in only 14.28% of the patients included in the study; Most patients were diagnosed with the occasion of a UTI episode (40.87%);
- The most common reno-ureteral malformation is urinary tract dilation due to pielo-ureteral junction obstruction (PUJO), vesicoureteral junction obstruction (VUJO), vesicoureteral reflux (VUR), which was present in 119 patients out of a total of 252 (47.22%), with a bilateral predisposition to ureteral damage ($p < 0.00001$);
- The most common renal malformation was renal dysplasia, found in 24 patients, with a right predisposition ($p = 0.012972$);
- Bladder/subvesical malformations are less common (16 patients), but are accompanied by increased complexity;
- Infectious complications are frequently associated with reno-ureteral malformative pathology. More than half of the patients included in the current study (53.35%) had characteristic UTI symptoms, but this could be documented with positive urine culture in only 36.11% of patients (91 patients);
- Chronic kidney disease was identified in 33 patients in the group (13.09%), more often in cases with bilateral or bladder/subvesical involvement;

- Malformative associations are common, so it is useful to identify CAKUT in children with musculoskeletal malformations (spina bifida), ear malformations, and genital malformations, these being the most common associations. In the current study, one in 10 patients with CAKUT subsequently had spina bifida. Also, the presence of spina bifida is a risk factor for surgical treatment necessity ($p = 0.0178$);

Our results encourage healthcare professionals to use antibiotics with caution and careful restraint. Effective treatment for recurrent UTIs in patients with CAKUT remains a medical challenge.

CAKUT pathology does not benefit from etiological drug treatment, but the prevention of infectious and degenerative complications can benefit from drug treatment. Effective treatment of infectious complications is vital because these patients have an increased risk of developing kidney scars or antibiotic resistance.

Surgical treatment remains a solution for cases with complex malformative pathology, for low urinary obstruction (bladder and subvesical malformations), for cases with significant dilatations, and those associated with VUR. Surgical techniques are useful when the medical benefits outweigh the risks. Surgical treatment performed as early as possible prevents the development of infectious complications and kidney injury, preserving kidney function.

A desirable goal is the use of a CAKUT patient monitoring algorithm and reaching a consensus on the pediatric patient monitoring and treatment guide with CAKUT.

Improving the addressability and adherence of patients to the monitoring scheme by understanding the main possible complications remains a needed target.

The current study is a unique study at the national level, due to its peculiarity for renal-ureteral malformative pathology of the child, especially in the study of antibiotic resistance of germs that cause complicated UTIs.

Early diagnosis is useful and necessary for long-term survival, reducing the risk of complications can be achieved through regular monitoring.

ORIGINALITY AND PERSONAL CONTRIBUTIONS

As a contribution of this research to the literature, we offer a detailed analysis of CAKUT types in pediatric patients and evolution patterns in the circumstances of a developing country, a continuous training medical team. This study's goal is to keep medical standards comparable to European guidelines. Similar research has revealed a much higher percentage of prenatal and/or neonatal diagnoses of CAKUT. Improving prenatal and neonatal diagnostic methods through routine use of abdominal US could increase early diagnosis of CAKUT.

The prevalence of UTIs is high, especially in the presence of risk factors such as malformative pathology. The growing antibiotic resistance of germs requires approaches aimed to limit the use of antibiotics on a large scale. Through the research methodology, the present project brings new, additional information about the loco-regional patterns of antibiotic resistance of uropathogens causing UTI in pediatric CAKUT patients. There are only a few studies of this type worldwide with which we can compare the data obtained, given that most of them refer to a pediatric research sample but without its particularization under the auspices of the presence of CAKUT.

Through this research, we propose the use of a diagnostic algorithm for pediatric patients with suspected reno-ureteral malformation, which stages step by step the data obtained and stratifies the risks for early medical intervention, as non-invasive as possible.

Also, we are proposing territorial and then national registries to monitor patients with CAKUT and treat complications as early as possible.

PERSPECTIVES

Early diagnosis of CAKUT using non-invasive imaging methods such as the abdominal US, as screening, both in the fetal period and in the early postnatal period (in the first 4-6 weeks of life) is a goal to be achieved.

It is recommended to perform an abdominal US for all children with febrile UTI regardless of age, but it brings the opportunity of an early CAKUT diagnosis. In case of recurrent UTIs, despite a normal abdominal US, further investigation like cystourethrography is indicated. Early identification and assessment of cases of renal injury through routine use of scintigraphy remain the perspective of the future. The implementation and use of the algorithms and guidelines described in the field, by mutual agreement, bring the national standards closer to the international ones.

The use of a common system of staging of renal-ureteral dilatation between the radiologist-imager, the pediatric nephrologist, the pediatric surgeon, and the family doctor is a desideratum of the medical community.

Media coverage and promoting the careful and moderate use of antibiotic therapy are essential to avoid increasing germ resistance.

The establishment of national registries of patients with CAKUT can increase the adherence to treatment and dispensary, implicitly decreasing the rate of complications.

Pediatric patients with CAKUT require regular monitoring:

- annual monitoring in patients with renal malformations (renal agenesis, renal hypoplasia, defects of position, or renal fusion) who do not associate infectious complications and maintain creatinine clearance (Cl) levels above 60ml/min (CKD stage I, II);
- every 6 months for patients with ureteral malformations who do not associate infectious complications or maintain creatinine Cl levels above 60ml/min CKD stage I, II);
- every 3 months for pediatric patients with CAKUT who have recurrent UTI or CKD, or associate bladder/subvesical malformations;
- monthly for patients with surgically uncorrected VUR, associated with UTI or CKD in advanced stages (IV, V).

Monitoring and managing the patient with CAKUT remains the responsibility of a multidisciplinary team, consisting of a family physician, pediatrician, radiologist, pediatric nephrologist, and pediatric surgeon.